REMARKS

Upon entry of the above amendment, claims 1-7, 15-20, 22, 23 and 42 will be pending in the present application. Applicants respectfully submit that neither the claim amendments nor the new claim add any new matter within the meaning of 35 USC §132. Accordingly, entry of these amendments is respectfully requested.

1. Rejection of claims 1-6, 15-16, 18-23 and 42 under 35 U.S.C. §103(a)

The Official Action states that claims 1-6, 15-16, 18-23, and 42 are rejected under 35 U.S.C. §103(a) as being unpatentable over Gilis *et al.* (WO 00/03697) and Ishibashi *et al.* (U.S. Patent Application No. 2003/0012815) in view of Lynenskjold *et al.* (U.S. Patent Application No. 2003/0211168) and Nara *et al.* (U.S. Patent No. 6,245,351).

As the basis for this rejection, the Official Action states in relevant part:

> Gilis *et al.* and Ishibashi *et al.* in view of Lynenskjold *et al.* and Nara *et al.* ...provide the teaching, suggestion and motivation to use any suitable solvent system in order to provide a working solution for coating core particles.

Response

Applicant respectfully traverses this rejection of claims 1-6, 15-16, 18-23, and 42. The cited references do not establish a *prima facie* case of obviousness against the presently pending claims.

To establish a prima facie case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court recently held in KSR International Co. v. Teleflex Inc. et al., Slip Opinion No. 04-1350, 550 U.S. (April 30, 2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building

blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (KSR, supra, slip opinion at 13-15). Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. Amgen Inc. v. Chugai Pharm. Co., 18 USPQ 1016, 1023 (C.C.P.A 1970). Lastly, the prior art references must teach or suggest all the limitations of the claims. In re Wilson, 165 USPQ 494, 496 (C.C.P.A. 1970).

A. Presently claimed subject matter

The present pending claims as exemplified by currently amended independent claim 1 are directed to:

> A method of manufacturing a water-insoluble azole antifungal active agent—oral dosage form, said method comprising the steps of: providing a single phase working solution comprising a water-insoluble azole antifungal active agent, water, a water-soluble polymer and a solvent, said solvent selected from the group consisting of alcohol, acetone, and mixtures thereof; providing core particles formed from a pharmaceutically acceptable material; combining said working solution with said particles to produce a water-insoluble azole antifungal active agent-coated particles; drying said water-insoluble azole antifungal active agent -coated particles; and forming said dried particles into an oral dosage form; wherein said working solution is essentially free of methylene

chloride, and said oral dosage form is essentially free of methylene chloride.

B. The Teachings of the Gilis *et al.* reference (WO 00/03697)

The Gilis *et al.* reference teaches pellets having a core coated with an antifungal and a polymer. The pharmaceutical dosage form disclosed in the Gilis *et al.* reference is prepared using a suitable solvent system comprising a mixture of dichloromethane and an alcohol. The Gilis *et al.* reference specifically teaches that the solvent mixture should comprise at least 50% by weight of dichloromethane (see p. 9, lines 17-20). Further, the Gilis *et al.* reference does not disclose a working solution containing both the drug and water, as required by the present claims.

C. The Teachings of the Ishibashi *et al.* reference (U.S. Patent Application No. 2003/0012815)

The Ishibashi *et al.* reference discloses a sustained release formulation prepared by spray-coating a solution containing a hydrophobic organic substance-water-soluble polymer mixture onto a drug-containing core substance, followed by spray-coating a different hydrophobic organic compound-water-soluble polymer mixture onto the resulting coating layer. The

Ishibashi *et al.* reference teaches compositions formed by spraying a polymeric layer on top of a drug-containing core. This is different from the presently claimed process, which requires both the drug and the polymer in the same layer.

D. The Teachings of the Lynenskjold *et al.* reference (U.S. Patent Application No. 2003/0211168)

The Lynenskjold *et al.* reference teaches the production of spray-dried coated particles comprising an inert particulate carrier, a cellulosic binder, an active substance and water. Lynenskjold *et al.* teach the use of aqueous dispersions or solutions are preferred for the coating composition but alkanols (ethanol), ketones (acetone) and chlorinated hydrocarbons (methylene chloride) may also be used. None of the examples provided in the Lynenskjold *et al.* reference disclose the use of any of these solvents with water. This process of producing coated particles is different from the presently claimed process, which requires a water-insoluble azole antifungal, a water-soluble polymer, water and a solvent in the same working solution.

E. The Teaching of the Nara *et al.* reference (U.S. Patent No. 6,245,351

The Nara *et al.* reference teaches a drug core coated with a composition comprising a water-insoluble substance, a swellable polymer and, optionally, a hydrophilic substance dissolved or dispersed in a solvent where the solvent can be water, an organic solvent or mixtures thereof. The organic solvent can be ethyl alcohol or acetone. This is different from the presently claimed process, which requires both the drug and the polymer in the same layer.

F. The combination of references does not show all the elements of the pending claims in one working solution, and thus cannot render these claims obvious

The presently pending claims are distinguishable from the cited references. None of the references, taken alone or in combination, contain all the elements of the presently pending claims in the same working solution, and thus cannot render these claims obvious. In particular, independent claim 1 recites a single phase working solution comprising a water-insoluble azole antifungal active agent, water, a water-soluble polymer and a solvent, said solvent selected from the group consisting of alcohol, acetone and mixtures thereof, wherein said working solution is essentially free of methylene chloride,

and said oral dosage form is essentially free of methylene chloride (Emphasis added).

In contrast, Gilis *et al.* and Ishibashi *et al.* both disclose dichloromethane as a suitable solvent. Accordingly, the solvent system recited in the present application is different from the solvent systems disclosed in the Gilis *et al.* and Ishibashi *et al.* references. The Gilis *et al.* reference does disclose that dichloromethane levels should be limited, however, the reference teaches away by including 50% dichloromethane in the solvent system. Nothing in the Gilis *et al.* reference suggests a solvent system that does not include dichloromethane. Further, the Gilis *et al.* reference teaches that azole antifungal compounds are sparingly soluble in water, and that other non-aqueous based systems must be used in order to solubilize the compounds (see p. 1, lines 9-34).

The Ishibashi *et al.* reference teaches that solvents should be selected according to the hydrophobic organic compound and water soluble polymer used. However, the Ishibashi *et al.* reference discloses the use of dichloromethane and carbon tetrachloride as suitable solvents, which are specifically excluded from the presently pending claims. Further, the Ishibashi *et al.* reference does not state how to reduce or

eliminate the levels of dichloromethane to the extent taught by the present application. Therefore, the Ishibashi *et al.* reference does not remedy the deficiencies of the Gilis *et al.* reference.

Regarding the Lynenskjold *et al.* reference, this reference teaches the production of spray-dried coated particles comprising an inert particulate carrier, a cellulosic binder, an active substance and water, while the presently pending independent claim 1 teaches a working solution comprising a water-insoluble azole antifungal active agent, water, a water soluble polymer and a solvent, said solvent selected from the group consisting of alcohol, acetone, and mixtures thereof. Lynenskjold *et al.* disclose that organic solvents can be used in the composition but an aqueous solution or dispersion is preferred. The organic solvent can be methylene chloride, ethanol or acetone. Lynenskjold *et al.* does not teach or suggest the combination of water and an organic solvent along with the water soluble polymer. The examples in the reference do not include organic solvents along with water in the production of the particulate compositions. Therefore, Lynenskjold does not remedy the deficiencies of Gilis *et al.* or Ishibashi *et al.* as it shows a different solvent system that does not contain all

the elements in the same working solution as required by the presently pending claims.

The Nara *et al.* reference teaches a drug core coated with a coating composition comprising a water-insoluble substance, a swellable polymer and, optionally, hydrophilic substances dissolved or dispersed in a solvent. While the solvents can be water, an organic solvent or mixtures thereof, this solvent system does not include a water-insoluble azole antifungal active agent or any other active agent. The presently pending claims require that the solvent system and the drug be in the same working solution and, in turn, be present in the same coating layer on the core particle. Therefore, Nara *et al.* does not remedy the deficiencies of Gilis *et al.* or Ishibashi *et al.* or Lynenskjold *et al.* as it does not show a coating solution that contains an active agent in the working solution as required by the presently pending claims.

None of the cited references disclose a working solution containing the drug, water-soluble polymer, solvent, and water, wherein the working solution is essentially free of methylene chloride as required by the present claims. Therefore, it would have been unexpected for a person having ordinary skill in the art to use water and an organic solvent for a water-insoluble

drug. Further, Ishibashi *et al.* and Nara *et al.* both teach compositions formed by spraying a polymeric layer on top of a core substance containing a drug. In contrast, the presently claimed process requires both the drug and the polymer to be contained in the same layer.

Accordingly, the Gilis *et al.*, Ishibashi *et al.*, Lynenskjold *et al.*, and Nara *et al.* references, taken alone or in combination, do not show all of the elements of the presently pending claims in the same working solution, and thus cannot render these claims obvious.

G. No motivation exists to combine the references and thus cannot render these claims obvious

The Examiner asserts in the Office Action that the applicant is attacking the references individually by pointing out how specific claim limitations are not met by the individual references. However, as noted in this response, the references, taken alone or in combination, do not teach each and every element of the presently claimed subject matter. In addition, the Examiner has established no motivation to combine the references.

With regard to motivation to combine references, **MPEP 2143**

discusses the requirements of a *prima facie* case of obviousness. First, there must be some suggestion or motivation to combine the reference teachings or to modify the reference, and second, there must be a reasonable expectation of success. Finally, the prior art reference or references when properly combined must teach or suggest all the claim limitations.

Regarding motivation to modify properly combined references, **MPEP 2143.01** states that a proposed modification cannot render the prior art unsatisfactory for its intended purpose. If it does, then there is no suggestion or motivation to make the proposed modification. Further, the proposed modification cannot change the principle operation of a reference.

In *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, Federal Circuit, *No.* 06-1325 (June 28, 2007), the Federal Circuit rejected Alphapharm's argument that the prior art would have led one of ordinary skill in the art to select compound b as a lead compound most promising to modify in order to improve its antidiabetic activity and thus potentially arrive at the claimed pioglitazone. The district court considered three references in reaching its determination, namely Takeda's '200 patent; Sodha II; and Takeda's '779 patent. The district court

found that Sodha II taught away from compound b and that any suggestion in the '779 patent to select compound b was essentially negated by the disclosure of Sodha II in view of the more exhaustive and reliable scientific analysis presented by Sodha II and the teaching away. Accordingly, the Federal Circuit accorded more weight to the Sodha II reference.

It is submitted that a *prima facie* case of obviousness has not been established because the Gilis *et al.*, Ishibashi *et al.*, Lynenskjold *et al.* and Nara *et al.* references fail to teach or suggest all of the limitations of the presently pending claims as required by *In re Wilson*. Further, a *prima facie* case of obviousness has not been established because the skilled artisan would have no motivation to modify Gilis *et al.* or Ishibashi *et al.* to incorporate the solvent system of Lynenskjold *et al.* or the solvent coating system of Nara *et al.*

Gilis *et al.* teaches a bead core coated with a very sparingly water-soluble drug and a hydrophilic polymer. The Ishibashi *et al.* reference teaches a drug core coated with a coating layer of a hydrophobic substance and a water-soluble polymer. Neither reference includes water in their respective coating layers. Lynenskjold *et al.* and Nara *et al.* each teach a coating composition that contains water. One of ordinary skill

in the art would not substitute the solvent system of Lynenskjold *et al.* or Nara *et al.* containing water with that of Gilis *et al.* or Ishibashi *et al.* Gilis et al. and Ishibashi et al. provide no motivation to provide water in their coating systems for a very sparingly soluble active agent and hydrophobic substance, respectively. Therefore, one of ordinary skill in the art would not look to Lynenskjold et al. or Nara et al. for a solvent system containing water to dissolve a very sparingly water-soluble active agent or a hydrophobic substance.

In further support, applicants respectfully submit that the process of the presently pending claims provides particles that have increased solubility under pH 5.0 dissolution conditions, resulting in enhanced bioavailability of the active ingredient. Table 5 on page 24 of the present specification shows that the azole antifungal composition had a dissolution rate increase by 129% over the dissolution profile of the commercial product SPORANOX® under fasted conditions. The table further shows that the dissolution rate increased by 74% over the commercial product under fed conditions.

Further, the Supreme Court in KSR reiterated the framework for determining obviousness that was stated in Graham v. John Deere Co. 383 U.S. 1, 148 USPQ 459 (1966). The four factual

inquiries that were recited in Graham are as follows: (1) Determining the scope and contents of the prior art; (2) Ascertaining the differences between the prior art and the claims in issue; (3) Resolving the level of ordinary skill in the pertinent art; and (4) Evaluating evidence of secondary considerations, such as unexpected results. Id. As stated in **MPEP 2141**, secondary considerations such as unexpected results must be considered in every case in which they are present.

Accordingly, if the Examiner insists on maintaining that a prima facie case of obviousness has been established against the presently pending claims, applicants respectfully submit that they have successfully rebutted this finding of obviousness by demonstrating unexpectedly superior results for the claimed subject matter. In this regard, applicants respectfully direct the Examiner's attention to Table 5 on page 24 of the present specification, showing an unexpectedly superior dissolution profile over the commercial product. Accordingly, the presently claimed subject matter is not obvious in view of the references cited by the Examiner.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the current rejection to presently pending claims 1-6, 15, 16, 18-20, 22, 23 and 42.

2. Rejection of claim 7 under 35 U.S.C. §103(a)

The Official Action states that claim 7 is rejected under 35 U.S.C. §103(a) as being unpatentable over Gilis *et al.* (WO 00/03697) and Ishibashi *et al.* (U.S. Patent Application No. 2003/0012815) in view of Lynenskjold *et al.* (U.S. Patent Application No. 2003/0211168) and Nara *et al.* (U.S. Patent No. 6,245,351) as applied to claims 1-6, 15-16, 18-23, and 42 above, and further in view of Vladyka *et al.* (U.S. Patent No. 6,497,905).

As the basis for this rejection, the Official Action states in relevant part:

> Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to provide the claimed azole antifungal agent in the amorphous state because Vladyka *et al.* teach that these agents having low aqueous solubility will benefit from providing them in their amorphous state. The skilled artisan would reasonably expect that an azole antifungal agent in its amorphous state will exhibit increase solubility (Vladyka *et al.*, col. 5, lines 20-25) in the aqueous coating solutions as motivated and suggested by Gilis *et al.*, Ishibashi *et al.*, Lynenskjold *et al.*, and Nara *et al.* as discussed *supra*.

Response

Applicant respectfully traverses this rejection of claim 7. The cited references do not establish a *prima facie* case of obviousness against the presently pending claims.

The teachings of Gilis *et al.*, Ishibashi *et al.*, Lynenskjold *et al.*, and Nara *et al.* are discussed above in Section 1, the contents of which are hereby incorporated by reference in their entirety. None of these references teach the active agent in an amorphous form.

The Vladyka *et al.* reference teaches a solid solution of an azole compound in an amorphous state dissolved in a molten solution of a hydrophobic vehicle, a stabilizing agent, a disintegrant and optionally a binder. This composition is formulated by melting the hydrophobic vehicle at a temperature above its melting point but below that of the azole compound and dissolving the azole compound in the hydrophobic vehicle, followed by a granulation and cooling step. In contrast, the presently pending claims require a working solution comprising a water-insoluble azole antifungal, a water-soluble polymer, water and a solvent that is coated onto a carrier particle. The process of the presently pending claims is completely different from the process taught by Vladyka *et al.* In addition, the

process of Vladyka *et al.* is completely different from the references whose deficiencies it is meant to cure. None of the Gilis *et al.*, Ishibashi *et al.*, Lynenskjold *et al.*, and Nara *et al.* references teach a melt granulation process to form a solid solution, as required by Vladyka *et al.*

Vladyka *et al.* does not cure the deficiencies of Gilis *et al.*, Ishibashi *et al.*, Lynenskjold *et al.*, and Nara *et al.* as it does not teach that an amorphous drug can be contained in a solution of water-soluble polymer, water and a solvent to be sprayed onto a core particle. In addition, there is no motivation to combine the teachings of Vladyka *et al.* with those of Gilis *et al.*, Ishibashi *et al.*, Lynenskjold *et al.*, and Nara *et al.* because one of ordinary skill in the art would not look to a reference teaching granulation of a melted solid solution to substitute components with a solution containing a water soluble polymer, water and a solvent to be coated onto a particle.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the current rejection to presently pending claim 7.

3. Rejection of claim 17 under 35 U.S.C. §103(a)

The Official Action states that claim 17 is rejected under 35 U.S.C. §103(a) as being unpatentable over Gilis *et al.* (WO 00/03697) and Ishibashi *et al.* (U.S. Patent Application No. 2003/0012815) in view of Lynenskjold *et al.* (U.S. Patent Application No. 2003/0211168) and Nara *et al.* (U.S. Patent No. 6,245,351) as applied to claims 1-6, 15-16, 18-23, and 42 above, and further in view of Martindale: The Complete Drug Reference (Pharmaceutical Press, London, 2002, pages 1344-1349).

As the basis for this rejection, the Official Action states in relevant part:

> Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use any known surfactant, such as those taught by Martindale, in the manufacture of azole antifungal-coated particles. Gilis *et al.* teach that surfactants can be incorporated in pharmaceutical preparations comprising azole antifungal agents. As such, the skilled artisan would have been imbued with at least a reasonable expectation that the surfactants taught in Martindale would be amiable for use in coating methods suggested and motivated by the cited references.

Response

Applicant respectfully traverses this rejection of claim 17. The cited references do not establish a *prima facie* case of obviousness against the presently pending claims.

The teachings of Gilis *et al.*, Ishibashi *et al.*, Lynenskjold *et al.*, and Nara *et al.* are discussed above in Section 1, the contents of which are hereby incorporated by reference in their entirety. None of these references teach the surfactants recited in Claim 17.

The Martindale reference is cited by the Examiner to show that various surfactants, some of which are recited in Claim 17, are suitable for use in pharmaceutical formulations. While the Martindale reference does recite surfactants that are suitable for use in pharmaceuticals, it fails to cure the other deficiencies of Gilis *et al.*, Ishibashi *et al.*, Lynenskjold *et al.*, and Nara *et al.* as none of the references alone or in combination teach a process of coating a core particle with a working solution of a water insoluble azole antifungal, a water soluble polymer, water and a solvent wherein the solvent is an alcohol, acetone or a mixture thereof.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the current rejection to presently pending claim 17.

CONCLUSION

In view of the foregoing, applicants respectfully request the Examiner to withdraw the pending rejections and allow all pending claims 1-7, 15-20, 22, 23 and 42 to proceed to grant. If the Examiner has any questions or wishes to discuss this matter, she is welcomed to telephone the undersigned attorney.

Respectfully submitted,
THE NATH LAW GROUP

By: _____
Gary M. Nath
Registration No. 26,965
Joshua B. Goldberg
Registration No. 44,126
Customer No. 20529

Date: August 18, 2008
THE NATH LAW GROUP
112 South West Street
Alexandria, VA 22314
(703)-548-6284

GMN/JBG/RMJ:ROA.doc